NATIONAL INSTITUTES OF HEALTH
Evidence-based Methodology Workshop on
Polycystic Ovary Syndrome
December 3–5, 2012

DRAFT EXECUTIVE SUMMARY

The NIH workshop is sponsored by the Office of Disease Prevention and the Eunice Kennedy Shriver National Institute of Child Health and Human Development. A multidisciplinary steering committee developed the workshop agenda. The NIH Library created an extensive, descriptive bibliography on polycystic ovary syndrome (PCOS) to facilitate workshop discussion. During the 2½-day workshop, invited experts discussed the body of evidence, and attendees had opportunities to provide comments during open discussion periods. After weighing the evidence, an unbiased, independent panel prepared this report that summarizes the workshop and identifies future research priorities.

Introduction

Polycystic ovary syndrome (PCOS) is a common hormone disorder that affects approximately 5 million women of reproductive-age in the United States. Women with PCOS have difficulty becoming pregnant (i.e., are infertile) due to hormone imbalances. One such imbalance is high blood levels of androgens, which can come from both the ovaries and the adrenal gland. Other organ systems that are affected by PCOS include the brain, pancreas, liver, muscle, blood vasculature, and fat.

In addition to fertility impairment, other common symptoms and findings of PCOS include:

- Irregular or no menstrual periods in women of reproductive age (ovulatory dysfunction)

- Acne
- Weight gain
- Excess hair growth on the face and body (hirsutism)
- Thinning scalp hair
- Ovarian cysts (polycystic ovarian morphology)
- Mental health problems.

Women with PCOS are often resistant to the biological effects of insulin and, as a consequence, may have high insulin levels. Women with PCOS are at risk for type 2 diabetes, high cholesterol, and high blood pressure. Obesity also appears to worsen the condition. Costs to the U.S. health care system to identify and manage PCOS are approximately $4 billion annually; however, this estimate does not include treatment of the serious conditions associated with PCOS.

For most of the 20th century, PCOS was a poorly understood condition. In 1990, the National Institutes of Health (NIH) held a conference on PCOS to create both a working definition of the disorder and diagnostic criteria. The outcome of this conference, the *NIH Criteria*, served as a standard for researchers and clinicians for more than a decade. In 2003, a consensus workshop in

Rotterdam in the Netherlands developed new diagnostic criteria, the *Rotterdam Criteria*. The Androgen Excess (AE) and PCOS Society proposed the *AE-PCOS Criteria* in 2006.

On December 3–5, 2012, the NIH sponsored the Evidence-based Methodology Workshop on Polycystic Ovary Syndrome. The panel was asked to clarify:

1. The benefits and drawbacks of different diagnostic criteria

2. The causes, predictors, and long-term consequences of PCOS

3. Optimal prevention and treatment strategies.

1. Benefits and Drawbacks of Different Diagnostic Criteria

Over the past 2 decades, the use of the *NIH Criteria*, the *Rotterdam Criteria*, and the *AE-PCOS Society Criteria* have been useful in understanding the syndrome. The individual components of these criteria are difficult to measure, and it is not clear how each contributes to the outcomes of concern. Table 1 shows the criteria proposed by these authoritative bodies. Table 2 demonstrates the problem of overlapping and nonexclusive phenotypes by the three currently used classification criteria. The use of multiple classification systems is confusing and delays progress in understanding the syndrome. It also hinders the ability of clinicians to partner with women to address and manage the health issues that concern them. Each of these diagnostic criteria has inherent strengths and weaknesses (see Table 3).

Table 1. Diagnostic Criteria for PCOS

NIH 1990	Rotterdam 2003	AE-PCOS Society 2006
• Chronic anovulation • Clinical and/or biochemical signs of hyperandrogenism (with exclusion of other etiologies, e.g., congenital adrenal hyperplasia) *(both criteria needed)*	• Oligo- and/or anovulation • Clinical and/or biochemical signs of hyperandrogenism • Polycystic ovaries *(two of three criteria needed)*	• Clinical and/or biochemical signs of hyperandrogenism • Ovarian dysfunction (Oligo-anovulation and/or polycystic ovarian morphology)

Table 2. Potential Phenotypes of PCOS by NIH 1990, Rotterdam 2003, and AE-PCOS 2006

		Potential PCOS Phenotypes									
		A	B	C	D	E	F	G	H	I	J
Panel Terminology	**Diagnostic Criteria**	NIH						AE-PCOS/Rotterdam 1			Rotterdam 2
Androgen Excess	Hyperandrogenemia	+	–	+	+	–	+	+	–	+	–
	Hyperandrogenism*	+	+	–	+	+	–	+	+	–	–
Ovulatory Dysfunction	Oligo-anovulation	+	+	+	+	+	+	–	–	–	+
Polycystic Ovarian Morphology	Polycystic Ovaries	+	+	+	–	–	–	+	+	+	+
	NIH 1990 Criteria	X	X	X	X	X	X				
	Rotterdam 2003 Criteria	X	X	X	X	X	X	X	X	X	X
	AE-PCOS 2006 Criteria	X	X	X	X	X	X	X	X	X	

Modified from Azziz, R., et al. The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report. *Fertility and Sterility* 91(2): 456–488, 2009.

*Clinical signs or symptoms of excess androgen

Table 3. Strengths and Limitations of Diagnostic Criteria

Diagnostic Criteria	Strength	Limitation
Androgen Excess	• Included as a component in all major classifications • A major clinical concern for patients • Animal models employing androgen excess resembling but not fully mimicking human disease	• Measurement is performed only in blood. • Concentrations differ during time of day. • Concentrations differ with age. • Normative data are not clearly defined. • Assays are not standardized across laboratories. • Clinical hyperandrogenism is difficult to quantify and may vary by ethnic group. • Tissue sensitivity is not assessed.
Ovulatory Dysfunction	• Included as a component in all major classifications • A major clinical concern for patients • Infertility a common clinical complaint	• Normal ovulation is poorly defined. • Normal ovulation varies over a woman's lifetime. • Ovulatory dysfunction is difficult to measure objectively.
Polycystic Ovarian Morphology	• Historically associated with syndrome • May be associated with hypersensitivity to ovarian stimulation	• Technique dependent • Difficult to obtain standardize measurement • Lack of normative standards across the menstrual cycle and lifespan (notably in adolescence) • Technology required to accurately image not universally available • Imaging possibly inappropriate in certain circumstances (e.g., adolescence)

2. Causes, Predictors, and Long-Term Consequences of PCOS

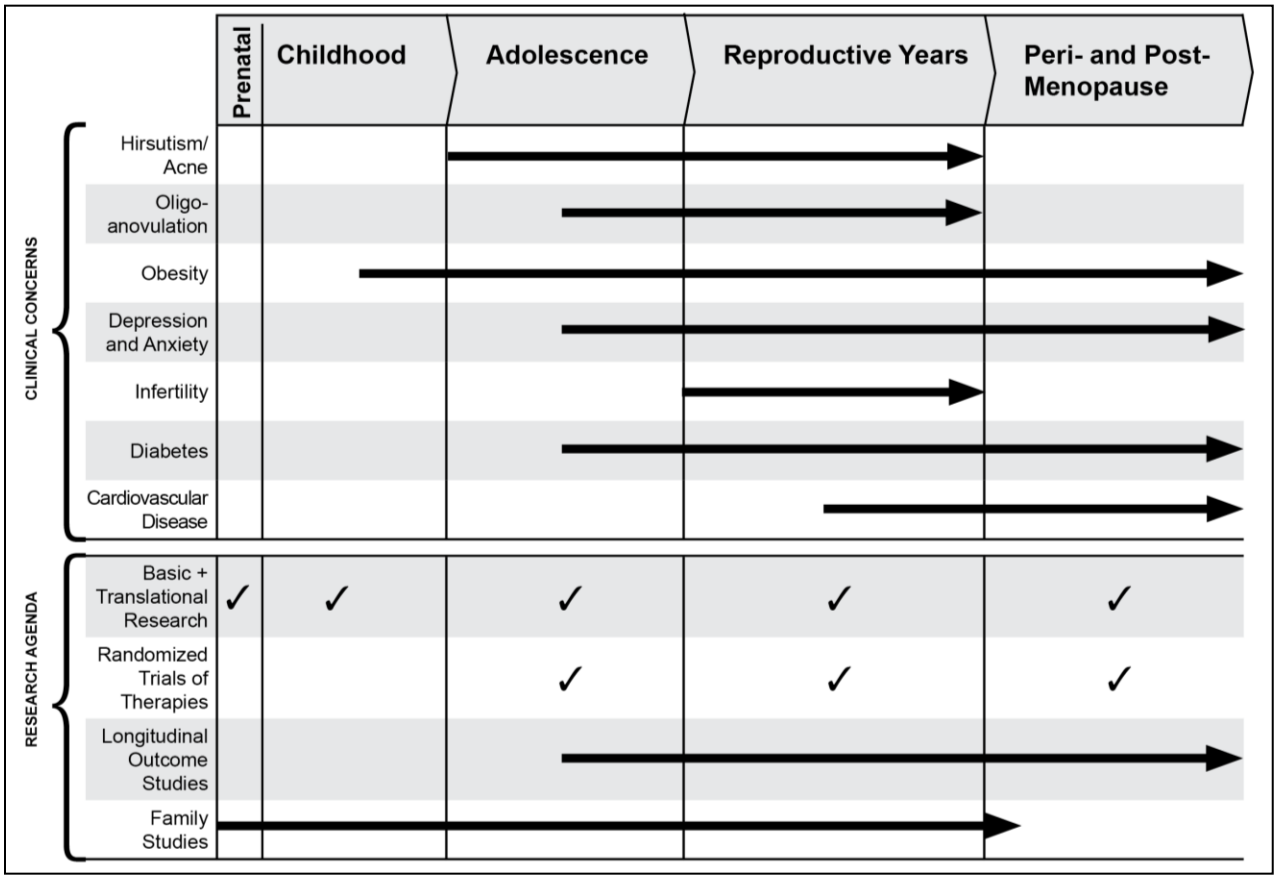
The etiology of the syndrome is multifactorial and involves interactions between "nature" and "nurture." Androgens appear to be clearly implicated in the pathogenesis based on animal models and clinical presentation. Prenatal testosterone exposure in animal models results in many, but not all, of the characteristics of this syndrome.

A variety of observations, including concordance in monozygotic twins, strongly suggests a genetic component. Recent genome-wide association studies (GWAS) have identified candidate genes that merit further study. Epigenetic factors and environmental factors, such as obesity, appear to exacerbate any underlying genetic predisposition. The extent to which obesity or its associated insulin resistance contributes to the syndrome, independently or collectively, is not known.

The impact of the syndrome on an individual varies significantly based on several factors, such as the severity of the components, comorbidities, and life course considerations. In addition, each individual experiences the syndrome in the context of her own reproductive health, metabolic, and quality of life concerns (see Table 4). Hirsutism, obesity, and infertility are common complaints. This syndrome is also associated with metabolic dysfunction, including diabetes. However, it is unclear whether these abnormalities increase the incidence of cardiovascular events or other diabetic complications. The relationship between the syndrome and other metabolic abnormalities, sleep apnea, depression, anxiety, and quality of life remains to be

defined by longitudinal studies. Given the prevalence of this syndrome worldwide, these important public health issues deserve more attention.

Table 4. Common Clinical Manifestations Associated with the Syndrome Across the Life Course and Types of Research Recommended



The PCOS Australian Alliance evaluated the quality of the published evidence on PCOS in 2011 and published a 1,100-page evidence appraisal document based on 22 separate systematic reviews and more than 38,000 articles from around the world (www.managingpcos.org.au/pcos-evidence-based-guidelines).

3. Optimal Prevention and Treatment Strategies

Because the underlying pathophysiology of PCOS is not fully determined, treatment is currently directed at symptoms rather than targeting a specific etiologic pathway. Lifestyle modification and weight reduction have been shown to decrease androgen effects, increase ovulation, and improve insulin sensitivity. Metformin decreases androgen levels but has not demonstrated effect on fertility and has little effect on insulin action. Preliminary studies suggest that thiazolidinediones improve insulin action but do not alter ovarian function. Clomiphene and aromatase inhibitors increase fertility but can lead to multiple pregnancy and do not alter other metabolic or psychosocial manifestations of the syndrome. Surgery has been shown to improve fertility and transiently affect ovarian function. Ovarian hyper-stimulation syndrome (OHSS) is a potentially *fatal* risk of advanced reproductive therapies in women with PCOS. Anti-androgens may mitigate but do not resolve hirsutism.

Continuous positive airway pressure (CPAP) treats obstructive sleep apnea (OSA) and may ameliorate metabolic dysfunction. However, it is not known if any of these treatments alter the natural history of this syndrome or its components. It is also not known whether screening for and subsequent treatment of associated abnormalities, such as OGTT[*]-diagnosed diabetes, reduces chronic morbidity or mortality.

[*] Oral glucose tolerance test

In summary, the panel has identified the following major areas as critical in the advancement of our understanding of the syndrome.

Panel Recommendations

1. We believe the name "PCOS" is a distraction and an impediment to progress. It causes confusion and is a barrier to effective education of clinicians and communication with the public and research funders. The name focuses on a criterion—polycystic ovarian morphology—which is neither necessary nor sufficient to diagnose the syndrome. We believe it is time to recognize the advances that have been made since the description of the syndrome by Irving F. Stein, Sr. and Michael L. Leventhal. It is time to expeditiously assign a name that reflects the complex metabolic, hypothalamic, pituitary, ovarian, and adrenal interactions that characterize the syndrome—and their reproductive implications. The right name will enhance recognition of this major public health issue for women, educational outreach, "branding," and public relations and will assist in expanding research support.

2. We recommend maintaining the broad, inclusionary diagnostic criteria of Rotterdam (which includes the "classic NIH" and AE-PCOS criteria) while specifically identifying the phenotype:

    - Androgen Excess + Ovulatory Dysfunction

- Androgen Excess + Polycystic Ovarian Morphology

- Ovulatory Dysfunction + Polycystic Ovarian Morphology

- Androgen Excess + Ovulatory Dysfunction + Polycystic Ovarian Morphology

The specific phenotypes should be reported explicitly in all research studies and clinical care. This recommendation should be disseminated to journal editors, funding sources, and professional societies.

3. We recommend the following:

    a. Improve the methods and criteria used to assess androgen excess.

        - Develop a precise, accurate, and traceable assay for androgen levels.

        - Define normal ranges for different ethnic groups and age groups.

        - Record the conditions under which the sample is drawn (e.g., time of day, time of menstrual cycle).

        - Clearly define the criteria used for the clinical diagnosis of androgen excess, including variability based on ethnicity.

b. Improve the methods and criteria used to assess ovulatory dysfunction.

- Clearly define the criteria used to diagnose oligomenorrhea, amenorrhea, and anovulation.

- Establish normal ranges across the age spectrum and across populations.

c. Improve the methods and criteria used to assess polycystic ovarian morphology.

- Develop methods to define polycystic morphology accurately and precisely.

- Establish normal ranges across the age spectrum and across populations.

4. We believe that the involvement of consumers in the guideline development of the Australian task force and the engagement of primary care providers, multidisciplinary teams, and patients in education and programmatic roll-out is a model worthy of imitation.

5. We recommend several important research and clinical priorities:

    a. Conduct adequately powered, carefully phenotyped, multiethnic cohort studies to establish the genetic or epigenetic cause(s) of the syndrome.

    b. Establish the prevalence of abnormal glucose tolerance in women wishing to conceive, and determine whether treatment of abnormal glucose tolerance prior to or early post-conception alters maternal-fetal outcomes.

    c. Conduct translational research to determine the mechanisms by which the syndrome alters ovarian, hypothalamic-pituitary-adrenal, and metabolic function to establish model systems that can be used to identify novel therapeutic approaches.

    d. Conduct appropriately powered multiethnic longitudinal studies to determine:

        i. If the syndrome is associated with increased cardiovascular and diabetic complications.

        ii. If the risk of these cardiovascular and diabetic complications (or the lack thereof) is associated with specific phenotypes.

iii. If treatment of metabolic abnormalities reduces the risk of cardiovascular and diabetic complications.

e. Conduct suitably powered studies to determine if the syndrome is associated with endometrial, breast, and ovarian cancers, and, if so, determine optimal prevention, detection, and treatment.

f. Identify optimal therapies to treat the most common symptoms and patient complaints of the syndrome, such as hirsutism and obesity.

g. Identify optimal therapies to achieve successful pregnancy.

6. Establish multidisciplinary programs to improve public and health care provider awareness and management for women who currently have the syndrome.